Unusual reactions in molecules with crowded functional groups: sulfonamide reduction under oxidizing conditions in camphor derivatives

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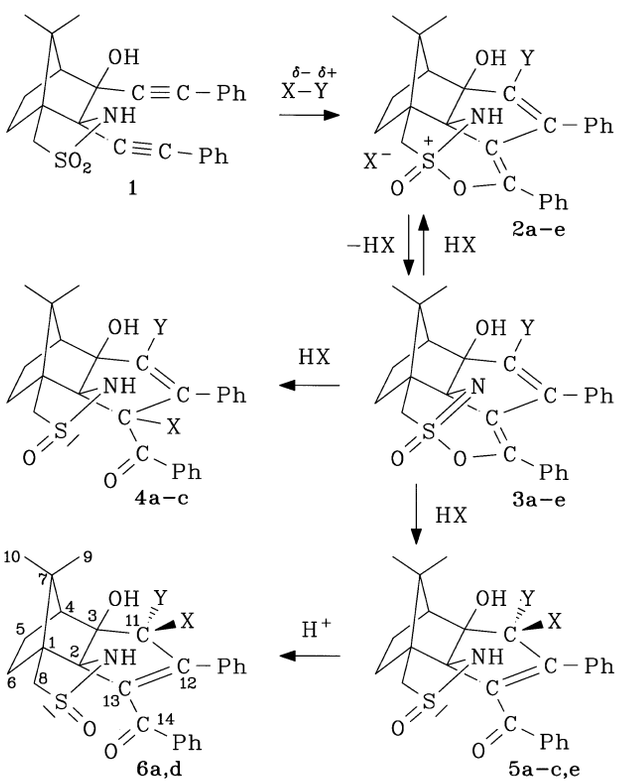
The reaction of the camphor-derived dialkyne 1 with polarizable compounds like acids and halogens leads to the formation of cationic species of the type 2 with a pentacyclic structure. These are stable in trifluoroacetic acid, but undergo reduction of the sulfonamide to a sulfinamide group in other solvents. The reaction mechanism was studied by NMR measurements. With iodine as reagent, further reactions occur due to the low stability of the carbon–iodine bonds, leading to the introduction of a carbonyl group into the newly formed carbocyclic ring. The crystal structure of the acetate derivative 8 shows that the reduction of the sulfonamide group occurs stereoselectively, leading to the *S*-configuration of the sulfur atom in the sulfinamide. This configuration can be inverted by strong acids. In addition, reduction of the sulfinamides to a sulfenamide was observed in the reaction mixture with iodine.

Introduction

Functional group transformations are the basis of organic chemistry. Reading standard textbooks, one may get the impression that all is known about the fate of a given functional group under specified conditions. However, standard reactions may fail if strain or steric hindrance exert a dominant influence. We wish to show in this paper how the expected course of a reaction changes when several functional groups are crowded together in close vicinity. We chose compounds with alkynyl groups as these are of interest with respect to the ene-diyne class of antibiotics.[1] Camphor-derived diynes like **1** are inert towards non-polar reagents, but readily react with polarizable molecules like halogens under cationic cyclization to form a new five-membered ring fused with the bornane skeleton. By NMR spectroscopy we found as key intermediates cations with the positive charge at the sulfur atom of the sulfonamide group. Semiempirical calculations supported this result.[2] This type of cyclization with annulation of five-membered rings may occur also with other compounds having two alkynyl groups at a suitable distance and in a suitable orientation.[3] The camphor derivative **1** not only contains two phenylacetylene moieties but also a sulfonamide and a hydroxy group in very close vicinity. For most of the reactions discussed here, the NH group of the sulfonamide is essential; they do not occur if the nitrogen is blocked by a methyl group or complexation with a metal ion.[2]

Results and discussion

The reaction of an electrophile, such as a proton, with the sulfonamide **1** leads directly, without any intermediate detectable by NMR, to a cyclic cation of the type **2** stabilized by the transfer of the positive charge to the sulfur atom[2] (Scheme 1). We studied the formation and subsequent reactions of such cations by NMR spectroscopy (mainly ^{1}H NMR), which allowed us not only to identify intermediates but also to follow the kinetics of the reactions. Trifluoroacetic acid is the reagent of choice for the investigation of cations as it stabilizes positive charges by solvation with the non-nucleophilic trifluoromethyl group.[4] Thus, the cation **2a** (Y = D) is formed on dissolution of **1** in CF_3CO_2D; the protonation occurs with pseudo-first-order



Scheme 1 Reaction of the dialkyne **1** with a: X–Y = CF_3CO_2H (or CF_3CO_2D), b: X–Y = Br_2, c: X–Y = Cl–I, d: X–Y = Cl–H, e: X–Y = I_2 NMR numbering of the compounds

kinetics. From NMR, one can estimate the rate constant as 0.07 min^{-1}. The cation is stable in this solution for at least 3 days, without any change in the NMR spectra, and the assignment of the NMR signals is possible with the help of COSY, ROESY, HMQC and HMBC techniques (for NMR numbering, see Scheme 1; NMR data are found in Tables 1 and 2 for all compounds where a complete assignment was possible). A remarkable feature is the large separation (>1 ppm) of the diastereotopic 8-H protons, compared with the starting material or

Table 1 ^{1}H NMR data [δ values; multiplicity, integration and coupling constants (Hz) in brackets] of new compounds at 360.134 MHz in $CDCl_3$. Numbering as that of the corresponding carbon atoms shown in Scheme 1

	4 (d)	5,6 (m)	8 (2 d)	9,10 (2 s)	11 (s)	Phenyl	Other
2a[c]	2.13 (4.5)	1.63 (1 H), 1.84 (1 H), 2.05 (2 H)	3.09, 4.16 (15.1)	1.09, 1.55	6.15 (1 H)	6.74 (d, 2 H, 7.1), 6.89 (m, 4 H), 6.94 (d, 2 H, 7.8), 7.01 (t, 1 H, 7.8) 7.14 (t, 1 H, 7.8)	3.92 (s, 1 H) 5.08 (s, 1 H)
2b	2.36 (4.5)	1.50 (1 H), 1.94 (2 H), 2.15 (1 H)	3.84, 4.45 (14.9)[a]	1.11, 1.54	—	6.92–7.26 (m)	*b*
2c	2.32 (4.6)	1.56 (1 H), 1.92 (2 H), 2.09 (1 H)	3.61, 4.08 (11.7)[a]	1.08, 1.56	—	6.89–7.10 (m)	5.70 (s, br, 2 H)
4b	2.22 (4.5)	1.43 (1 H), 1.86 (2 H), 2.46 (1 H)	3.09, 3.41 (13.6)	0.94, 1.17	—	7.20 (m, 6 H), 7.63 (d, 2 H, 7.2), 7.78 (d, 2 H, 7.8)	*b*
4c	2.26 (5.2)	1.51 (1 H), 1.96 (2 H), 2.61 (1 H)	3.13, 3.50 (13.6)	1.03, 1.25	—	7.17 (m, 6 H), 7.52 (d, 2 H, 7.5), 7.73 (d, 2 H, 7.0)	*b*
5b	2.42 (4.5)	1.17 (1 H), 1.85 (3 H)	2.56, 3.99 (13.6)	1.02, 1.65	—	7.07 (m, 5 H), 7.20 (m, 1 H), 7.50 (d, 2 H, 7.6), 7.57 (d, 2 H, 7.9)	3.75 (s, br, 1 H) 4.73 (s, 1 H)
5c	2.36 (5.2)	1.21 (1 H), 1.89 (1 H), 1.99 (2 H)	2.60, 3.94 (13.6)	1.07, 1.64	—	7.17 (m, 6 H) 7.44 (d, 2 H,7.6), 7.55 (d, 2 H, 7.4)	*b*
6a[d]	2.14 (4.0)	1.12 (1 H), 1.86 (2 H), 2.28 (1 H)	2.91, 3.19 (14.0)	0.96, 1.20	5.22 (1 H)	7.16 (m, 3 H), 7.20 (t, 2 H, 7.5), 7.36 (t, 1 H, 7.5) 7.44 (m, 2 H), 7.89 (dd, 2 H, 8.4, 1.0)	6.23 (s)
6c	2.07 (4.6)	*e*	3.18, 3.54 (13.6)	0.96, 1.21	—	*e*	*b*
6d	2.01 (5.0)	1.05 (1 H), 1.83 (2 H), 2.25 (1 H)	3.10, 3.52 (13.5)	0.99, 1.20	5.32 (1 H)	7.17 (m, 3 H), 7.24 (t, 2 H, 7.7), 7.36 (t, 1 H, 7.3), 7.47 (m, 2 H) 7.85 (d, 2 H, 6.3)	3.90 (s, br, 1 H) 5.28 (s, 1 H)
7	2.23 (4.5)	1.53 (1 H), 1.92 (2 H), 2.01 (1 H)	3.15, 3.57 (13.6)	1.01, 1.49	—	6.85 (m, 6 H) 7.00 (m, 4 H)	3.53 (s, br, 1 H), 5.33 (s, br, 1 H)
8	2.47 (5.0)	1.17 (1 H), 1.95 (1 H), 2.05 (1 H) 2.18 (1 H)	2.65, 3.87 (14.0)	1.08, 1.63	—	7.18 (m, 3 H), 7.35 (m, 4 H), 7.43 (m, 1 H), 7.81 (dd, 2 H, 8.6, 1.0)	2.33 (s, 3 H) 4.44 (s, 1 H)
9	2.31 (4.5)	1.08 (1 H), 1.93 (1 H), 2.03 (2 H)	2.69, 3.87 (14.3)	1.03, 1.73	—	7.17 (m, 5 H), 7.33 (m, 2 H), 7.40 (m, 1 H), 7.64 (d, 2 H, 7.8)	3.85 (s, br, 1 H) 4.70 (s, br, 1 H)
10	2.18 (4.8)	1.14 (1 H), 1.81 (1 H), 2.07 (1 H) 2.49 (1 H)	3.03, 3.06 (10.3)	1.01, 1.51	—	7.21 (m, 3 H), 7.32 (m, 4 H), 7.43 (t, 1 H, 7.8) 7.86 (dd, 2 H, 8.1, 1.0)	3.04 (s, 1 H) 3.83 (s, 1 H)
11	2.10 (5.2)	1.10 (1 H), 1.83 (1 H), 1.95 (1 H) 2.37 (1 H)	3.21, 3.60 (14.3)	0.95, 1.18	—	7.19 (m, 5 H), 7.34 (m, 3 H), 7.75 (dd, 2 H, 8.4, 1.0)	4.20 (s, 1 H) 6.06 (s, 1 H)
12	2.20 (4.9)	1.08 (1 H), 1.90 (1 H), 2.05 (1 H) 2.51 (1 H)	3.35, 3.75 (13.7)	1.06, 1.55	—	7.20 (m, 4 H), 7.25 (m, 1 H), 7.35 (m, 3 H) 7.70 (dd, 2 H, 8.4, 1.0)	3.62 (s, 1 H) 5.22 (s, 1 H)

[a] During the reaction, signal broadening and highfield shift occurs. [b] Not detected. [c] Measured in CF_3CO_2D. [d] Measured in $(CD_3)_2CO$. [e] Not assigned due to overlap.

other products of cyclization, together with the downfield shift of one of the protons (δ = 3.09 and 4.16). This suggests that the positive charge is mainly localized at the sulfur atom, in close vicinity to C-8. Remarkably, no trace of any product from typical alkyne reactions which may occur under acidic conditions, *e.g.* the Rupe rearrangement, was observed with **1**. Cations similar to **2a** were readily detected by NMR in the reaction of **1** with other reagents (bromine, **2b**; iodine monochloride, **2c**) in $CDCl_3$, but they are less stable and undergo further reactions. With iodine, the formation of the cation is quite slow and its reactivity high, and thus it could not be detected in the complex reaction mixture.

Sulfonamides normally react with electrophiles such as protons, carbocations, or metal ions at the nitrogen atom. The cleavage of the sulfur–nitrogen bond often occurs as a consequence. For the formation of a bond between a carbocation and an oxygen atom of a *sulfonamide* group, we could not find any precedence in the literature. What has been observed is the formation of a carbon–oxygen bond in the intramolecular reaction of a carbocation with a *sulfone*.[5] Here, the oxygen is clearly the most nucleophilic part of the functional group. In our case, the higher nucleophilicity of the nitrogen atom is more than compensated by the close vicinity of one oxygen atom of the sulfonamide to the carbocation, making the oxygen atom the logical partner for the bond formation.

The stability of **2a** is limited to the trifluoroacetic acid solution; an attempt to isolate it by evaporation of the solvent led to a mixture containing three new compounds. When stored in $CDCl_3$ solution, two of them rearranged to a final product which could be isolated and identified as **6a** (Y = H from CF_3CO_2H). With bromine and iodine monochloride, compounds were observed (and isolated for bromine) from the reaction of the cations **2b**,**c** which have spectra very similar to those of the two compounds unstable in the case of trifluoroacetic acid [**4a**: $\delta(CDCl_3)$ 2.92 (d, *J* 4.4 Hz, 4-H), 3.20, 3.30 (2 × d, *J* 13.6 Hz, 8-H), 6.56 (s, 11-H) and 1.13, 1.20 (2 × s, 9-H, 10-H); **5a**: $\delta(CDCl_3)$ 2.26 (d, *J* 4.9 Hz, 4-H), 2.87, 4.14 (2 × d, *J* 13.5 Hz, 8-H), 5.15 (s, 11-H) and 1.04, 1.59 (2 × s, 9-H, 10-H); compare with Table 1]. We assign to them the structures **4a**–**c** and **5a**–**c**. The puzzling common feature of the compounds **4**–**6** is

Table 2 ^{13}C NMR data (δ values) of new compounds at 90.556 MHz in $CDCl_3$. Numbering of the carbon atoms follows Scheme 1

	1	2	3	4	5,6	7	8	9,10	11	12	13	14	Ph (C_q)	Ph (CH)
2a[a]	57.9	80.3	92.5	53.4	24.3 27.0	53.6	50.8	20.9 21.4	140.1	127.7	126.1	154.0	131.9 142.5	127.7, 128.4 128.5, 129.3 129.7, 131.9
4b	68.0	87.5	90.1	57.1	22.8 23.9	49.7	55.3	23.8 23.9	138.0	147.7	133.0	194.8	134.2 138.2	127.1, 127.6 127.7, 128.3 128.7, 128.8
4c	66.8	88.1	89.1	56.5	22.8 26.8	49.1	53.4	23.6 23.6	140.1	163.2	148.3	195.1	132.7 137.3	128.1, 128.2 129.2, 129.5 129.9, 133.0
5b	68.1	87.5	90.2	57.1	23.5 28.8	49.3	56.0	24.0 26.7	80.2	138.6	153.2	195.3	131.6 137.8	128.1, 128.9 130.4, 130.6 133.0
5c	67.2	88.2	89.1	56.4	23.6 29.4	49.0	59.9	24.0 26.6	*c*	138.9	152.7	195.6	132.9 137.6	128.2, 128.4 129.0, 130.0 130.6, 133.3
6a[b,d]	64.8	91.6	95.4	50.1	21.7 25.4	50.8	58.0	21.5 22.0	87.9	139.4	143.6	196.4	133.0 136.5	127.8, 128.0 128.2, 128.8 129.7, 132.6
6d	67.5	83.5	91.8	53.2	21.6 26.7	51.1	58.7	23.4 23.4	73.4	139.6	145.9	196.6	132.8 137.8	128.1, 128.4 128.8, 129.1 129.8, 133.2
7	61.2	82.2	92.4	52.7	23.9 27.5	50.3	52.3	22.3 22.7	125.8	143.5	147.6	116.5	130.7 135.2	127.1, 127.6 127.7, 128.6
8[e]	64.4	88.4	89.9	52.7	21.8 28.5	52.6	55.0	22.9 24.5	201.4	160.2	140.1	197.5	128.8 135.7	128.3, 128.9 129.2, 129.7 134.5
9	63.9	85.2	89.1	53.8	22.8 28.1	52.9	55.7	23.0 25.0	205.9	162.4	140.1	197.9	128.8 135.2	128.4, 128.7 129.2, 129.3 129.7, 134.4
10	67.5	85.2	92.7	53.9	22.3 27.4	52.2	33.6	21.3 24.1	206.7	167.9	137.3	196.5	128.3 135.9	128.1, 128.7 128.9, 129.0 129.3, 133.7
11	66.0	84.9	87.3	51.0	21.0 26.0	52.5	58.3	22.8 23.0	205.5	165.3	139.4	197.1	128.8 135.9	128.3, 128.4 129.0, 129.4 129.8, 133.8
12	62.0	78.6	82.7	52.0	22.4 27.2	53.3	51.3	22.9 23.3	205.2	165.2	139.5	196.4	128.2 135.6	128.3, 128.4 128.8, 129.5 129.7, 134.1

[a] Measured in CF_3CO_2D. [b] Measured in $(CD_3)_2CO$. [c] Not detected. [d] Signals of the CF_3CO group not detected. [e] CH_3CO: 20.8, 171.7 ppm.

that they contain a *sulfinamide* group, *i.e.* a reduction of sulfur(VI) to sulfur(IV) has occurred, in the presence of (not yet completely consumed) oxidants such as halogens!

Sulfonamides are generally quite resistant towards reduction, and even with strong reducing agents such as lithium aluminium hydride, no reaction occurs; only the more reactive sulfonyl chlorides can be conveniently reduced to sulfinic acids.[6,7] Other sulfonic acid derivatives such as esters and anhydrides are converted by strong reducing agents into sulfur(II); sulfur(IV) products were rarely detected,[8] while sulfonamides generally remain inert. The only exception is the electrochemical reduction, where sulfinic acids are obtained from sulfonamides.[9] Reductions starting with the reaction of a sulfur compound with an electrophile are known only for sulfoxides and sulfones (*e.g.* the well-known Pummerer reaction), but not for sulfonamides where the nitrogen is the most nucleophilic part of the functional group. The synthesis of sulfinamides by reductive means normally employs sulfoximines as starting materials, which are much easier to reduce[10,11] (for a review of synthetic methods, see ref. 12). Only very few reactions are known where a sulfonamide is reduced under comparatively mild conditions, *e.g.* the photoisomerization of a saccharine derivative where oxygen is transferred to nitrogen.[13]

A plausible mechanism for our reaction involves the cation **2** as key intermediate where the existence of the carbon–oxygen bond should greatly facilitate the sulfonamide reduction. Attack of a nucleophile at either C-11 or C-13 could then initiate the sulfur–oxygen bond cleavage, leading to the observed products **5** or **4**. However, sulfur reduction occurs only if the sulfonamide is secondary; only the annulation of the five-membered ring to the bornane skeleton has been observed for *N*-methylated derivatives of **1** or its complexes with metals.[2] Thus, the NH group is essential. The rationale for this result is a deprotonation step leading to the neutral compound **3**, which we consider as the ultimate intermediate in the reduction process. Compound **3** must be in equilibrium with the cation **2** in comparatively low concentration and cannot be observed by NMR as such but only by its effect on the chemical shift and lineshape of H-8 in the cations **2b**,**c**. During NMR kinetics (for quantitative evaluation, the range 2.5–5.0 ppm is best suited), a considerable upfield shift (~0.6 ppm) accompanied by line broadening of these signals occurs as **2** disappears due to the subsequent reaction (Fig. 1). This is indicative of a decrease of positive charge at the sulfur atom because of the deprotonation, together with a proton exchange between **2** and **3** which is rapid on the NMR time-scale.

Compounds **3** may be considered as anti-Bredt compounds in the sense defined by Köbrich[14] where the sulfur occupies the bridgehead position. To see if the torsion of the S–N double bond in the anti-Bredt compounds might account for the higher reactivity of the neutral compounds **3** towards nucleophiles compared with the cations **2**, we calculated the bond lengths of the sulfur atom to its neighbours in the cation **2a**, the intermediate **3a**, the acyclic cation $[S(=O)(OMe)(Me)(NHMe)]^+$, and the acyclic neutral compound S(=O)(Me)(OMe)(=NMe) with PM3. The differences of the bond lengths in the cations are quite low and within the error of the calculation (*e.g.* for the S–N bond 1.737 Å in **2a** *vs.* 1.736 Å in the acyclic cation), while the neutral compounds show somewhat longer endocyclic bonds in the anti-Bredt compound **2a** (1.670 Å *vs.* 1.649 Å for S=N, 1.727 Å *vs.* 1.713 Å for S–O). In contrast, the exocyclic S=O bond in **2a** is shorter than the analogous bond in the acyclic

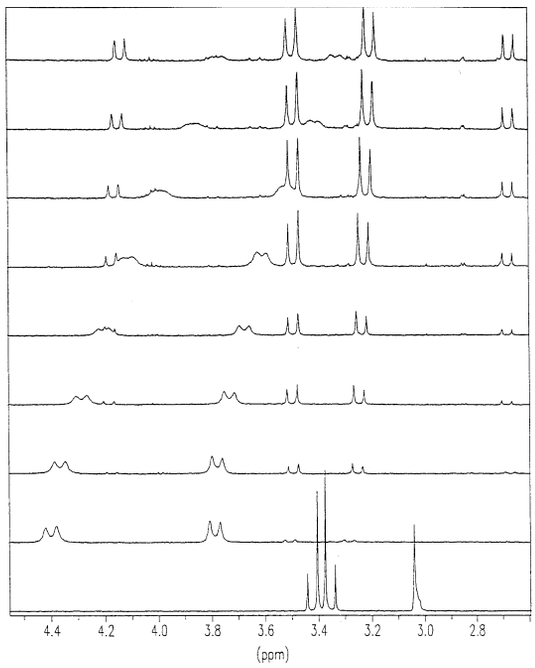
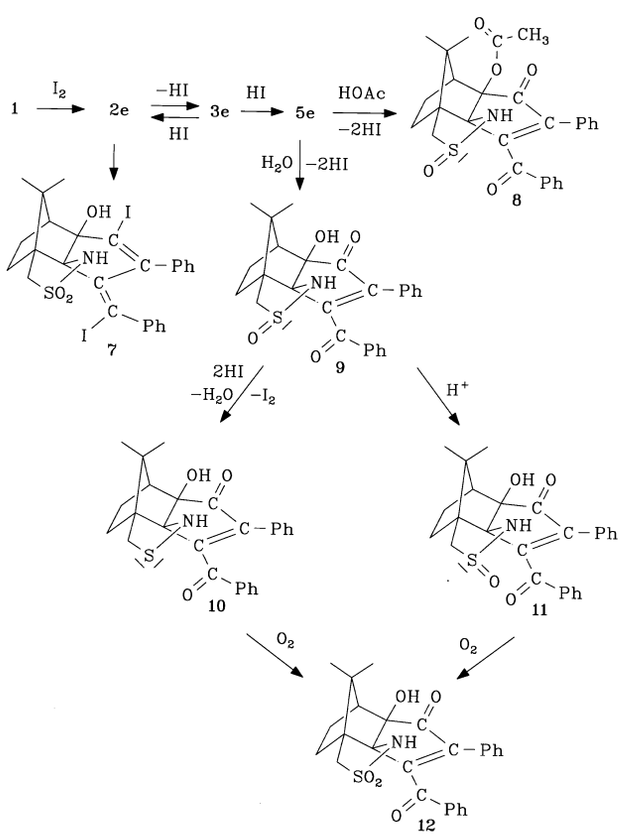


Fig. 1 NMR kinetics of the reaction of **1** with bromine. From bottom to top: $t = 0$, 1.5, 12, 22, 28, 32, 37, 42, 47 min; cation **2b**: 8-H signals shifting from 4.40 (d) to 3.78 (s, br) and from 3.79 (d) to 3.10 (s, br); **4b**: 3.50 (d), 3.22 (d); **5b**; 4.12 (d), 2.70 (d). The chemical shifts quoted in Table 1 are of the isolated compounds and therefore not exactly the same.



Scheme 2 Reaction of **1** with iodine

compound (1.452 Å *vs.* 1.474 Å). The differences reflect the strain imposed on the neutral compounds **3** by the introduction of the S=N double bond and might therefore explain its enhanced reactivity towards nucleophiles.

The two direct reduction products **4** and **5** could be isolated in the case of bromine, but are unstable in the case of iodine-

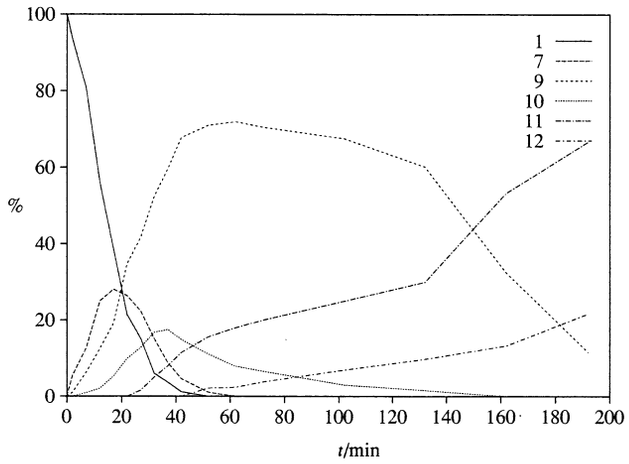


Fig. 2 Kinetics of the reaction of **1** with iodine

containing reagents. In aprotic solution, **4** is generally the less stable compound which starts to rearrange to **5** by an unknown mechanism. Thus, we could not determine the configuration of C-13 in the compounds **4**. It should be noted that the configuration of the sulfur atom in both types of compounds follows from the reduction mechanism and is therefore consistently *S* (for confirmation by crystal structure analysis, see below). However, in the presence of a strong proton acid (trifluoroacetic acid or HCl), an inversion of the configuration at sulfur occurs, leading to the thermodynamically more stable compounds of the type **6**. When gaseous HCl is bubbled through a toluene solution of **1**, **6d** with *R* configuration of the sulfur atom is the sole product. In the compounds **6a** (Y = H) and **6d**, the carbon atom C-11 bears a hydrogen atom and thus allows the determination of the configuration by NOE measurements. In the ROESY spectrum, both compounds show strong crosspeaks between 11-H and 4-H, as well as between 11-H and *endo*-5-H, which is possible only if the configuration at C-11 is *S*.

For the racemization of sulfinamides, a radical chain mechanism involving homolytic cleavage of the sulfur–nitrogen bond was suggested and experimentally confirmed for aromatic sulfinamides.[15] In our case, the inversion of the configuration of the sulfur atom in compounds of the type **5** occurs only in the presence of strong proton acids, and thus another mechanism involving protonation at the oxygen atom and addition of a nucleophile to the sulfur atom followed by Berry pseudorotations and elimination,[16] explains the observations much better (for a review of stereochemistry at sulfur, see ref. 17).

A very special case is the reaction of **1** with iodine (see Scheme 2). Because of the low bond-energy of carbon–iodine bonds, the isolation of intermediates containing iodine is difficult. The results of typical NMR kinetics are shown in Fig. 2. To the first detectable product, we assign the structure **7** (diiododialkene) because of the close similarity to the analogous compounds obtained with *N*-methylated products.[2] The compound is formed by attack of iodide at C-14 of the cation **2e** (which is not observable because of its very low concentration) and cannot be isolated in pure form. It disappears within 60 min from the reaction mixture. From the mass balance we conclude that it contributes to the increase in the concentration of the ketone **9** during this time. In this ketone the sulfur has already been reduced to the sulfinamide stage. It is the second major product observed in the kinetics and formed by hydrolysis of **5e** by traces of water. Only when rigorously dried $CDCl_3$ (P_4O_{10}) is used for the kinetic run, were signals observed which can be attributed to the primary product **5e** of the reduction process (8-H: $\delta = 2.60$ and 4.13 ppm, 2 × d, 14.2 Hz; compare Table 1); the 8-H pattern with the very large (up to 1.6 ppm) separation of the two diastereotopic protons (exceeding even the separation in the cations **2**) is typical of the sulfinamides **5** with *S*-configuration of the sulfur atom, while the separation is less

Table 3 Selected bond lengths (Å) and angles (degrees) for compound **8** (two crystallographically independent molecules)

S(1)–O(1)	1.478(2)	1.479(2)	O(1)–S(1)–C(8)	107.9(1)	107.8(1)
S(1)–N(1)	1.694(2)	1.689(2)	O(1)–S(1)–N(1)	109.1(1)	110.7(1)
S(1)–C(8)	1.832(2)	1.827(2)	S(1)–N(1)–C(2)	116.7(1)	117.1(2)
N(1)–C(2)	1.451(2)	1.460(2)	S(1)–C(8)–C(1)	109.5(2)	109.0(2)
C(1)–C(2)	1.572(3)	1.573(3)	N(1)–C(2)–C(1)	105.2(2)	105.0(2)
C(2)–C(3)	1.568(3)	1.567(3)	N(1)–C(2)–C(3)	118.4(2)	118.9(2)
C(2)–C(13)	1.529(3)	1.526(3)	N(1)–C(2)–C(13)	112.7(2)	112.2(2)
C(3)–C(11)	1.529(3)	1.530(3)	C(2)–C(3)–C(11)	105.2(2)	105.2(2)
C(1)–C(8)	1.517(3)	1.517(3)	C(2)–C(13)–C(12)	114.3(2)	114.6(2)
C(13)–C(12)	1.337(3)	1.341(3)	O(5)–C(11)–C(3)	124.6(2)	124.5(2)
C(11)–O(5)	1.206(2)	1.209(2)	C(3)–C(11)–C(12)	108.1(2)	108.3(2)
C(13)–C(14)	1.507(3)	1.504(3)	O(5)–C(11)–C(12)	127.3(2)	127.2(2)
C(12)–C(11)	1.484(3)	1.490(3)	C(13)–C(12)–C(11)	109.1(2)	108.9(2)
			N(1)–S(1)–C(8)	91.4(1)	91.8(1)

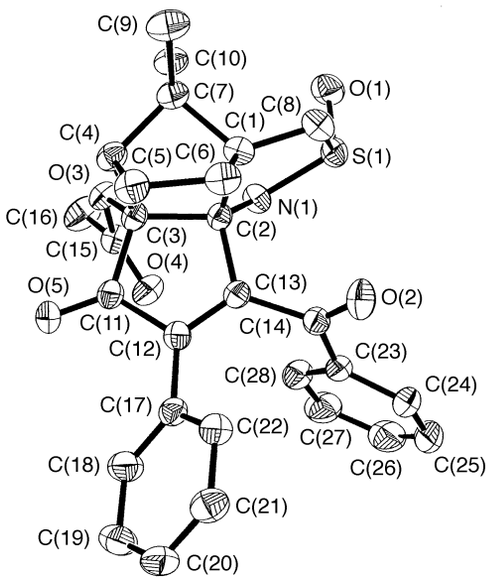


Fig. 3 Molecular structure of one of the crystallographically independent molecules of compound **8** with atomic numbering (ORTEP drawing, 50% probability, hydrogen atoms omitted for clarity)

in the compounds **6** with *R*-configuration. It is interesting to note that in a preparative run using methanol–acetic acid as solvent, the acetate **8** was obtained instead while the intermediate **7** (free OH group) was still present in the crude product mixture. The formation of an ester at the tertiary hydroxy group without concomitant formation of methyl acetate from the excess of methanol points to a very reactive intermediate. The formation of an oxirane in the position C(3)–C(11) by elimination of HI from **5e** might account for the observed products. It still contains an iodine at C-11 and could be attacked, after protonation by HI and ring opening, by the nucleophile (water or acetate). From compound **8**, we were able to grow crystals suitable for crystal structure analysis. Two crystallographically independent molecules which differ mainly in the orientation of the phenyl groups relative to the almost identical tetracyclic ring system were found in the unit cell. Fig. 3 shows one of them and its atom numbering, and Table 3 contains selected bond lengths and angles.

Although a tetracyclic skeleton is present in **8**, this does not impose much strain on the molecule. The bond lengths and angles in the five-membered carbocyclic ring formed during the initial cyclization do not deviate much from the geometry expected for a cyclopentenone, and there is enough space for the phenyl groups to be able to rotate freely in solution. Although not evident from the structure, the access of reagents to the double bond, C(12)–C(13), seems to be severely hindered; compounds **8**–**12** cannot be hydrogenated catalytically, nor does the double bond react with bromine or ozone. This indicates the absence of strain which should increase the reactivity of the functional groups in the ring system. In the heterocyclic ring, the bond lengths compare well with similar derivatives of camphorsulfonic acid; *e.g.* S(1)–N(1) [1.694(2) Å and 1.689(2) Å, respectively, for the two crystallographically independent molecules] with 1.685(3) Å in the palladium complex of a camphorsulfonylhydrazone,[18] or S(1)–C(8) [1.832(2)/1.827(2) Å] with 1.806(4) Å in the same complex or with 1.813(6) Å in the copper complex of a camphorsultam.[19] The bond angles reflect the quite relaxed geometry as well; the S(1)–N(1)–C(2) angle is 116.7(1)/117.1(1)° [110.2(3)° in the copper complex], and the N(1)–S(1)–C(8) angle 91.41(9)/91.79(9)° [98.1(1)° in a camphorsulfonyloxaziridine[20]]. The lower coordination number of sulfur in **8** has little influence on the geometry at this atom; the lone pair of the sulfur atom occupies almost as much space as an oxygen atom [angles O(1)–S(1)–N(1) 109.13(9)/110.7(1)°, compare with 108.7(2)/108.4(2)°,[18] 111.4(3)/114.3(3)°;[19] and O(1)–S(1)–C(8) 107.9(1)/107.8(1)°, compare with 111.8(2)/110.5(2)°,[18] 110.6(3)/107.7(3)°[19]]. The S(1)–O(1) bond [1.478(2)/1.479(2) Å] is a little longer than the S–O double bonds in sulfonamides [1.418(3)/1.429(3) Å,[18] 1.440(5)/1.442(5) Å,[19] 1.426(2)/1.428(2) Å[20]]. The configuration of the sulfur atom is *S*, the remaining oxygen atom at the sulfur atom pointing in the *exo* direction. The removed oxygen atom is now attached to C-14 forming the carbonyl group and quite far away from the sulfur atom [S(1)–O(2) distance 3.69 Å].

Although **9** is perfectly stable when isolated, further reactions occur during the kinetic measurements, as HI is present here. Already after 7 min a new isolable product forms which we identified as the sulfenamide **10**. The reduction of sulfur(IV) to sulfur(II) by HI is known for sulfinic acids,[21] but has not yet been reported for sulfinamides. A disproportionation of the sulfinamide to sulfenamide and sulfonamide can be excluded, as the sulfenamide appears earlier in the kinetics than the sulfonamide **12** (see below).

When isolated, **10** is stable towards air. In the kinetic mixture in the presence of oxygen and iodine, a slow reoxidation of the sulfenamide to a sulfinamide **11** different from **9** starts, having the inverse configuration at sulfur (*R*). This is an unprecedented reaction, as sulfenamides are normally over-oxidized to sulfonamides[22] or give other products.[23] The sulfinamide **11** corresponds to the compounds **6** observed in the reaction of **1** with strong protic acids. It seems that also in this case, **11** is the thermodynamically most stable of the isomeric sulfinamides (*ca.* 2.0 kcal mol^{-1} more stable than **9** according to a PM3 calculation). As HI is a strong acid, an additional source for **11** is the acid–nucleophile-catalyzed direct inversion of the configuration of the sulfur atom in **9**. The sulfinamides are stable towards air when isolated. However, on prolonged storage with oxygen available, the completely re-oxidized sulfonamide **12** is formed as the final product. A radical mechanism for the oxidation of sulfinic acids to sulfonic acids by molecular oxygen was demonstrated,[24] and this could also be the case here. Iodine itself is capable of oxidizing sulfinates to sulfonyl iodides,[25] but

no report on the oxidation of sulfinamides to sulfonamides by iodine exists. Product **12** can be obtained more conveniently by the reaction of **1** with iodine–dimethyl sulfoxide (DMSO) at high temperatures. This technique was claimed[26] to give diketones from alkynes, but this is obviously not the case here; we could not even reproduce the reported formation of diphenylethanedione from diphenylethyne, but obtained the over-oxidized product benzoic acid anhydride instead. For the preparation of **12**, the method works well. It can be assumed that the reaction occurs *via* the same pathways as outlined here for iodine, but at the high temperature applied, DMSO is able to oxidize all intermediates to **12**.

Conclusion

By assembling in close vicinity two alkynyl groups, a sulfonamide group and a tertiary alcohol group on a bornane skeleton a new and unexpected reaction occurred, namely, the stereoselective reduction of a sulfonamide to a sulfinamide under very mild conditions, even in the presence of oxidants like halogens. A very interesting application of the results obtained here would be a general synthetic method for the reduction of sulfonamides to sulfinamides [or even of other sulfur(VI) to sulfur(IV) compounds], *i.e.* the development of a reagent which would successfully effect such a reduction. The best way to accomplish such a task would be to construct a supramolecular ensemble from compounds able to include external sulfonamides in the ensemble, with functional groups capable of forming carbocations which come into close proximity with the sulfur atom. Work is in progress to investigate the formation of supramolecular ensembles containing sulfonamides and alkynes.

Experimental

NMR spectra were obtained with a Bruker AM 360 instrument (^{1}H: 360.13 MHz, ^{13}C: 90.56 MHz). Optical rotations were measured with a Perkin-Elmer 241 M polarimeter. $[a]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}. Mass spectra were measured with a Varian CH5 instrument (EI mode, 70 eV).

Semiempirical calculations were performed with PM3 using the standard parametrization as implemented in the HYPERCHEM software package. Geometry optimizations (Polak-Ribiere algorithm) were made before single point calculations.

The synthesis of the starting sulfonamide **1** has already been described.[2]

Kinetic measurements

The sulfonamide **1** (43 mg, 0.10 mmol) was dissolved in $CDCl_3$ (0.3 ml) and the solution transferred to an NMR tube. A solution of the reagent [bromine, iodine monochloride, or iodine (0.10 mmol)] in $CDCl_3$ (0.2 ml) was then added to it. CF_3CO_2D (0.5 ml) was used directly without a co-solvent. NMR measurements were started immediately afterwards and repeated first at 5-min intervals and later at larger intervals of time, until no further changes of the spectrum occurred during a period of 1 h. Cation **2a** is stable in trifluoroacetic acid solution for at least 3 d and has an optical rotation of $[a]_D^{23}$ +124 (*c* 1.7 in CF_3CO_2H).

Synthesis of the compounds 4b, 5b and 9–12

For preparative purposes, the appropriate reaction time for a maximum concentration of the desired product was determined from the kinetic experiments. Ten-fold quantities of starting materials were used, and the solvent $CDCl_3$ was replaced by a ten-fold amount of dichloromethane. At the end of the reaction, 10% aqueous sodium thiosulfate (10 ml) was added to the mixture, and the organic layer was separated and extracted with water (2 × 10 ml). After the organic layer had been dried ($MgSO_4$) it was evaporated and the crude product was purified as described for the individual cases.

(2*S*,3a*S*,6a*S*,9a*S*)-9-Benzoyl-7,9-dibromo-6a-hydroxy-10,10-dimethyl-8-phenyl-3,3a,4,5,6,6a-hexahydro-1*H*,9*H*-3a,6-methanoindeno[3a,4-*c*]-isothiazole 2-oxide 4b and (2*S*,3a*S*,6a*S*,-9a*S*)-9-benzoyl-7,7-dibromo-6a-hydroxy-10,10-dimethyl-8-phenyl-3a,4,5,6,6a,7-hexahydro-1*H*,3*H*-3a,6-methanoindeno-[3a,4-*c*]isothiazole 2-oxide 5b. Reagent bromine, reaction time 1 h. The products were separated by chromatography (silica gel, diethyl ether).

Compound **4b**: R_f 0.26, yield 0.34 g, 57%, mp 150 °C (decomp.) (Found: C, 53.5; H, 4.6; N, 2.1. Calc. for $C_{26}H_{25}Br_2NO_3S$: C, 52.8; H, 4.3; N, 2.4%); decomposes on attempted mass spectrometry.

Compound **5b**: R_f 0.13, yield 0.13 g, 27%, mp 140 °C (decomp.); $[a]_D^{23}$ +68.4 (*c* 0.4 in EtOH) (Found: C, 53.4; H, 4.8; N, 2.6. Calc. for $C_{26}H_{25}Br_2NO_3S$: C, 52.8; H, 4.3; N, 2.4%); decomposes on attempted mass spectrometry.

(2*S*,3a*S*,6a*S*,9a*S*)-9-Benzoyl-6a-hydroxy-10,10-dimethyl-8-phenyl-3a,4,5,6,6a,7-hexahydro-1*H*,3*H*-3a,6-methanoindeno-[3a,4-*c*]isothiazol-7-one 2-oxide 9 and (3a*S*,6a*S*,9a*S*)-9-benzoyl-6a-hydroxy-10,10-dimethyl-8-phenyl-3a,4,5,6,6a,7-hexahydro-1*H*,3*H*-3a,6-methanoindeno[3a,4-*c*]isothiazol-7-one 10. Reagent iodine, reaction time: 40 min. The products were separated by chromatography (silica gel, diethyl ether).

Compound **9**: R_f 0.18, yield 0.27 g, 60%, mp 235–238 °C; $[a]_D^{23}$ +291 (*c* 0.6 in EtOH) (Found: C, 69.6; H, 5.6; N, 3.0%; M^+, 447. Calc. for $C_{26}H_{25}NO_4S$: C, 69.8; H, 5.6; N, 3.1%; *M*, 447.6).

Compound **10**: R_f 0.80, yield 0.08 g, 18%, mp 248 °C (decomp.); $[a]_D^{23}$ +198 (*c* 0.3 in CH_2Cl_2) (Found: C, 72.0; H, 5.7; N, 3.1%; M^+, 431. Calc. for $C_{26}H_{25}NO_3S$: C, 72.4; H, 5.8; N, 3.2%; *M*, 431.6).

(2*R*,3a*S*,6a*S*,9a*S*)-9-Benzoyl-6a-hydroxy-10,10-dimethyl-8-phenyl-3a,4,5,6,6a,7-hexahydro-1*H*,3*H*-3a,6-methanoindeno-[3a,4-*c*]isothiazol-7-one 2-oxide 11. Reagent iodine, reaction time: 3 h. The product was isolated by chromatography (silica gel, diethyl ether), R_f 0.15, yield 0.22 g, 50%, mp 160–165 °C (decomp.); $[a]_D^{23}$ +132 (*c* 0.3 in CH_2Cl_2) (Found: C, 70.0; H, 5.8; N, 3.0%; M^+, 447. Calc. for $C_{26}H_{25}NO_4S$: C, 69.8; H, 5.6; N, 3.1%; *M*, 447.6).

(3a*S*,6a*S*,9a*S*)-9-Benzoyl-6a-hydroxy-10,10-dimethyl-8-phenyl-3a,4,5,6,6a,7-hexahydro-1*H*,3*H*-3a,6-methanoindeno-[3a,4-*c*]isothiazol-7-one 2,2-dioxide 12. (a) From kinetic experiments with iodine, compound **13** was isolated by chromatography (silica gel, diethyl ether) in 20% yield after a reaction time of >24 h. The compound can also be obtained by the iodine–DMSO procedure.[26]

(b) To a solution of compound **1** (430 mg, 1.0 mmol) in DMSO (5 ml) iodine (250 mg, 1.0 mmol) was added, and the mixture stirred for 1 h at 155 °C under nitrogen. 10% Aqueous sodium thiosulfate (20 ml) was added to the mixture which was then extracted with dichloromethane (3 × 20 ml). The combined extracts were dried (Na_2SO_4) and evaporated. The product was purified by chromatography (silica gel, dichloromethane–ethyl acetate, 2:1), R_f 0.47. Further purification was achieved by recrystallization form dichloromethane–hexane, yield 0.32 g, 70%, mp 278–280 °C; $[a]_D^{23}$ +170 (*c* 1.5 in EtOH). (Found: C, 67.4; H, 5.2; N, 3.1%; M^+, 463. Calc. for $C_{26}H_{25}NO_5S$: C, 67.4; H, 5.4; N, 3.0%; *M*, 463.6).

Synthesis of the compounds 6 and 8

(2*R*,3a*S*,6a*S*,7*S*,9a*S*)-9-Benzoyl-6a-hydroxy-10,10-dimethyl-8-phenyl-7-trifluoroacetoxy-3a,4,5,6,6a,7-hexahydro-1*H*,3*H*-3a,6-methanoindeno[3a,4-*c*]isothiazole 2-oxide 6a. The sulfonamide **1** (0.43 g, 1.0 mmol) was stirred with trifluoroacetic acid (5 ml) under nitrogen for 5 h. After evaporation of the bulk of solvent from the mixture, the residue was dissolved in dichloromethane (20 ml) and the solution stirred for 12 h. After evaporation of the solvent, the product was purified by chrom-

atography (silica gel, diethyl ether), R_f 0.18, yield 0.29 g, 54%, mp 235–236 °C, $[\alpha]_D^{23}$ −118 (*c* 0.6 in EtOH) (Found: C, 61.9; H, 5.2; N, 2.7%; M^+, 546. Calc. for $C_{28}H_{27}F_3NO_5S$: C, 61.5; H, 5.0; N, 2.6%; *M*, 546.6).

(2*R*,3a*S*,6a*S*,7*S*,9a*S*)-9-Benzoyl-7-chloro-6a-hydroxy-10,10-dimethyl-8-phenyl-3a,4,5,6,6a,7-hexahydro-1*H*,3*H*-3a,6-methanoindeno[3a,4-*c*]isothiazole 2-oxide 6d. A slow stream of dry HCl was bubbled through a solution of compound **1** (0.43 g, 1.0 mmol) in toluene (10 ml) for 1h. After being set once overnight, the mixture was evaporated and the residue purified by chromatography (silica gel, diethyl ether); R_f 0.36, yield 0.26 g, 56%, mp 188–190 °C (decomp); $[\alpha]_D^{23}$ −82.2 (*c* 0.8 in EtOH) (Found: C, 66.4; H, 5.4; N, 2.8%; M^+, 467 rel. ^{35}Cl. Calc. for $C_{26}H_{26}ClNO_3S$: C, 66.7; H, 5.6; N, 3.0%; *M*, 468.0).

(2*S*,3a*S*,6a*S*,9a*S*)-6a-Acetoxy-9-benzoyl-10,10-dimethyl-8-phenyl-3a,4,5,6,6a,7-hexahydro-1*H*,3*H*-3a,6-methanoindeno-[3a,4-*c*]isothiazol-7-one 2-oxide 8. To a solution of compound **1** (0.43 g, 1.0 mmol) in dichloromethane–methanol–acetic acid (1:1:1; 15 ml) was added iodine (0.25 g, 1.0 mmol) and the mixture stirred for 2 h. 10% Aqueous sodium thiosulfate (20 ml) and dichloromethane (20 ml) were added to the mixture after which the organic layer was separated, washed with water (2 × 10 ml), dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (silica gel, diethyl ether). Crystals suitable for X-ray crystallography were obtained by slow evaporation of an ethanolic solution; R_f 0.65, yield 0.24 g, 48%, mp 224–227 °C; $[\alpha]_D^{23}$ +274 (*c* 0.1 in EtOH) (Found: C, 68.9; H, 5.5; N, 2.9%; M^+, 489. Calc. for $C_{28}H_{27}NO_5S$: C, 68.7; H, 5.6; N, 2.9%; *M*, 489.6).

Crystal structure analysis of compound 8

Crystal data. $C_{28}H_{27}NO_5S$, $M_r = 489.59$, pale yellow crystals of dimensions 0.4 × 0.5 × 0.5 mm, orthorhombic, a = 14.940(1), b = 17.105(1), c = 19.032(1) Å, space group $P2_12_12_1$, $Z = 8$, $V = 4863.6$ Å^3 (by least-squares refinement on diffractometer angles of 25 automatically centred reflections), $D_{calc} = 1.337$ g cm^{-3}, $F(000) = 2064$; Mo-Kα radiation ($\lambda = 0.710\ 69$ Å), T = +23 °C.

Data collection and processing. Enraf Nonius CAD4 diffractometer, Mo-Kα radiation ($\lambda = 0.710\ 69$ Å), T = +23 °C; ω–θ scan mode with ω scan width = 0.80 + 0.35 tan θ. From 9624 measured [$(\sin\theta/\lambda)_{max} = 0.62$ Å^{-1}] and 9095 unique reflections ($R_{int} = 0.014$), 9089 were used for refinement. Data were corrected for Lorentz and polarization effects but not for absorption [μ(Mo-Kα) = 1.73 cm^{-1}]. During data collection, three standard reflections were measured periodically as a general check of crystal and instrument stability. No significant changes were observed.

Solution and refinement. Solution with direct methods using SHELXTL-PLUS.[27] Refinement by full-matrix least-squares on F^2 using SHELXL-93.[28] All hydrogen atoms were calculated in idealized geometry and allowed to ride on their corresponding C/N atom with isotropic contributions ($U_{iso(fix)} = 1.5 \times U_{eq}$ of the attached C/N). The non-H atoms were refined with anisotropic displacement parameters. The function minimized was $[\Sigma w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]^{1/2}$, with $w = q/\sigma^2(F_o^2) + (ap)^2 + (bp)$, $p = (F_o^2 + 2F_c^2)/3$, and $a = 0.0505$, $b = 1.09$. The structure converged for 631 refined parameters to *wR*2 and *R*1 (based on $\Sigma(|F_o| - |F_c|)/\Sigma|F_o|$) values of 0.0851 and 0.0352, respectively; [GOF = 1.028, absolute structure parameter = 0.01(5)]. Residual electron densities: +0.35/−0.27 e Å^{-3}. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/81.

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